Molten salts (ionic liquids) to improve the activity, selectivity and stability of the palladium catalysed Trost–Tsuji C–C coupling in biphasic media

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Abstract

AbstractThe Trost–Tsuji C–C coupling between ethyl cinnamyl carbonate and ethyl acetoacetate catalysed by a water soluble Pd/TPPTS catalyst (TPPTS = triphenylphosphine trisulphonate, sodium salt) and possible side reactions have been investigated in several biphasic media at 60–80°C. The use of the ionic liquid 1-butyl-3-methylimidazolium chloride as the catalytic layer brings definitive advantages over an aqueous catalytic phase: Palladium chloride may be used as the catalyst precursor, the solubility of the organic reagents is much higher which leads to faster reaction rates, the formation of cinnamyl alcohol is suppressed and common organic layers such as alkanes can be used with no noticeable catalyst deactivation. The yields in the C–C product up to 90% with TOF numbers of 23 h^{-1} may, thus, be achieved. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

The practical use of transition metal complexes as catalysts suffers from the difficulties encountered to separate the catalyst from the product after reaction [1]. This problem has been answered at the industrial scale in the case of olefin hydroformylation where the rhodium catalyst is dissolved in an aqueous layer by means of the TPPTS water soluble ligand [2–4]. Aqueous/organic biphasic catalysis is, nowadays, enjoying a great development and is applied to reactions as varied as carbonylation, hydrogenation, hydrocyanation, and other C–C coupling reactions [1]. Yet, some problems remain to be solved in biphasic catalysis: In the case where the substrate and reagents are poorly soluble in the aqueous catalytic phase, the reaction rate may turn to be far too slow for a realistic application. This is even more pronounced for fine chemical processes where substrates are often large organic molecules. Another problem concerns the side reactions that may develop with water as a reagent [5]. Co-solvents have been used successfully to increase substrate solubility in the

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aqueous phase [6,7]. The addition of triphenylphosphine in the organic layer during the biphasic hydroformylation of octene with a Rh/TPPTS (TPPTS = triphenylphosphinetrisulphonate, sodium salt) complex has been reported to increase the rate of reaction through a 'co-ligand' effect [8]. Other liquid media that are not miscible with a large variety of organic solvents such as ionic liquids (molten salts) and fluorocarbon compounds have been tested [9–16]. This report described some recent advances in the use of 1-butyl-3-methylimidazolium chloride (BMICl) as an ionic liquid medium for the nucleophilic allylic substitution (Eq. (1)) [17,18]. Thus, comparison with the well known organic/aqueous biphasic catalysis and the use of co-solvent is described, including the study of the side-reactions.

$$\text{(1)}$$
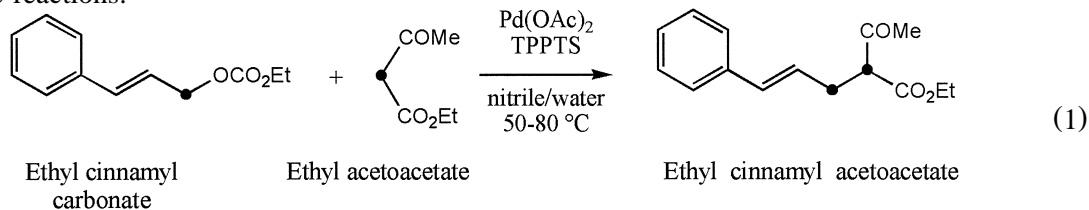
2. Experimental

2.1. Chemicals and analysis

The solvents were degassed but not further purified. The reagents ethyl acetoacetate (Aldrich, > 99%), cinnamyl alcohol (98%) palladium acetate (Aldrich, 98%), palladium chloride (Fluka, > 99%), 1-methylimidazole (Aldrich, > 99%) and butyl chloride (99.5%) were used as received. The substrate ethyl cinnamyl carbonate [19] and the ionic salt 1-butyl-3-methylimidazolium chloride [20] were prepared according to the literature procedures. All the catalyst preparations and catalytic tests have been performed under nitrogen. Samples of both the organic and the ionic liquid layers were quantitatively analysed by gas phase chromatography using dodecane as a standard [21]. The liquid–liquid partition coefficients, defined as the ratio of the organic layer concentration over the aqueous (molten salt) concentration, were estimated as previously reported [22,23].

2.2. Preparation of the catalyst and catalytic tests

Aqueous catalysts were prepared before each test according to the procedure described in the literature [24,25]. The ^{31}P NMR analysis of the catalyst before reaction was similar to reported data [25], and reveals the presence of Pd(TPPTS)$_3$ [26]. For the tests involving the ionic liquids, the catalyst was prepared by mixing TPPTS (0.475 g of a 30% wt. aqueous solution, 0.25 mmol) and palladium chloride (0.0088 g; 0.049 mmol). After 0.5 h of mixing at 60°C, the 1-butyl-3-methylimidazolium chloride (BMICl) (0.614 g; 0.51 ml; 3.52 mmol) was added. The water was then evacuated in vacuum for 0.5 h at 60°C. Addition of a solution of ethyl cinnamyl carbonate (0.126 g; 0.61 mmol) and ethyl acetoacetate (0.156 g; 1.20 mmol) in methylcyclohexane (2 ml) was the starting point of the catalytic test. The catalytic tests were performed in a well mixed batch reactor operating under chemical regime [23]. Because of the small scale preparation of the salt BMICl, the corresponding catalytic tests have been carried out in a 10-ml Schlenk tube in which chemical regime is not ensured [23]. TOF (h^{-1}) are defined as the ratio of mol of monoalkylated produced/mol of Pd/time to reach quantitative substrate conversion. When quantitative conversion was not achieved, extrapolation of the conversion vs. time was used to determine the TOF.

Table 1
^{13}C NMR data for the tri(m-phenylsulfonate)cinnamylphosphonium

	δ (ppm)	Attribution	J (Hz)
	118.32	C_i	$^1J_{PC} = 86$
	131.1	$C_{o \text{ or } o'}$	$^2J_{PC} = 9.7$
	132.0	$C_{o \text{ or } o'}$	$^2J_{PC} = 12.3$
	136.8	$C_{m'}$	$^3J_{PC} = 9.6$
	145.9	C_m	$^3J_{PC} = 12.6$
	131.1	C_p	$^4J_{PC} = 0$
	27.5	C_1	$^1J_{PC} = 43.8$
	141.0	C_2	$^2J_{PC} = 13.6$
	133.3	C_3	$^3J_{PC} = 10$
	135.7	C_4	$^4J_{PC} = 3.8$
	127.2	$C_{5 \text{ or } 6}$	-
	134.1	$C_{5 \text{ or } 6}$	-
	131.3	C_7	-

2.3. Characterisation of the catalytic layers by ^{31}P and ^{13}C NMR

A ^{31}P{^{1}H} NMR after reaction exhibits signals attributed to TPPTS oxide (34.6 ppm), Pd(TPPTS)$_2$(η^2-PhCHCHCH$_2$OH) (AB system at 28.3 and 26.3 ppm, $^2J_{PP} = 47$ Hz), cinnamyl phosphonium (s, 22.4 ppm) and the catalyst (s, 21.9 ppm). The ^{13}C{^{1}H} NMR analysis including a DEPT sequence allow the identification of the phosphonium (see Table 1) besides signals due to the TPPTS oxide. The phosphonium has been independently synthesised from the reaction of cinnamyl bromide with TPPTS in water. The ^{31}P{^{1}H} NMR spectrum of the molten salt catalytic phase after reaction displays the same pattern except for the AB peak system (see above) which does not appeared.

3. Results and discussion

A typical concentration vs. time profile for the reaction in the biphasic system butyronitrile/water is given in Fig. 1. As depicted, the C–C coupling product is formed in ca. 38% yield. The other identified products are cinnamyl alcohol (ca. 10%) and the bis alkylated side product (1 to 5% estimated from GC analysis). In a separate experiment, cinnamyl alcohol was shown to be a substrate for the reaction, although not as good as the carbonate, owing to the poorer living group properties of the hydroxide compared to carbonate [18]. That the hydroxide is not readily removed to yield the allyl complex is supported by the ^{31}P NMR investigation of the aqueous layer after reaction which depicts signals attributed to the Pd(0) olefinic complex Pd(TPPTS)$_2$(η^2-PhCHCHCH$_2$OH).

Knowing that all the organic reagents involved in the reaction are very poorly soluble in water (the partition coefficients $P = $ [organic layer]/[aqueous layer] is typically $< 1\%$), mass balance gives a yield of unknown product(s) of ca. 25%.

Another question arises from the shape of the profile at the early beginning of the reaction: a sharp decreases of substrate is noted while no consumption of the nucleophile ethyl acetoacetate is
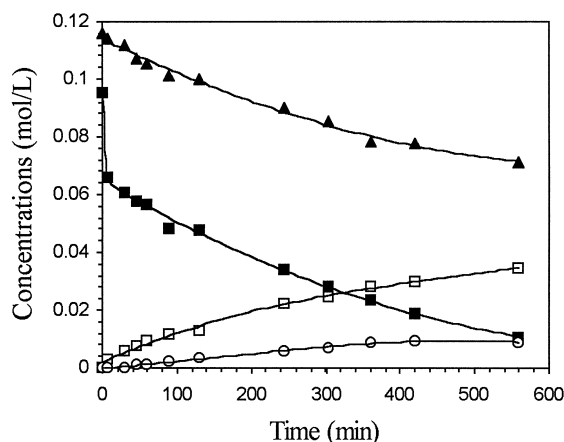
Fig. 1. Concentration in the organic layer vs. time (60°C, [Pd] = 0.01 mol l^{-1}, carbonate/Pd = 11, TPPTS/Pd = 5. Butyronitrile layer, 30 ml. Aqueous layer: 22 ml). Symbols: Ethyl cinnamyl carbonate (■), Ethyl acetoacetate (▲), Ethyl cinnamyl acetoacetate (□), Cinnamyl alcohol (○).

evidenced. These observations point to the formation of a water soluble side-product. Indeed, NMR analysis of the aqueous layer at the end of the reaction reveals peaks attributed to a phosphonium compounds, likely formed from the nucleophilic attack of the palladium π-allyl intermediates by the free TPPTS remaining in solution from the catalyst preparation. An authentic sample of the phosphonium has been prepared from the reaction of TPPTS with cinnamyl bromide. Thus, the 25% mass balance deficiency arises from this C–P coupling. Obviously, that phosphonium side product would not have been detected if the catalytic reaction would have been run at higher substrate/catalyst ratio than those typically used in the tests (ca. 10). However, operating at higher substrate/catalyst ratio would have resulted in prohibitive reaction time to achieve reasonable conversion because of the very slow reaction rate due to the very low solubility of the substrate in the aqueous layer. Thus, the biphasic butyronitrile/water catalytic system leads to two major problems: it gives cinnamyl alcohol as a by product and the very low solubility of the organic substrate into the aqueous layer precluded the use of high substrate/palladium ratio which indirectly resulted in the formation of the phosphonium (Scheme 1).

From a preliminary kinetic study, the rate of reaction of the palladium π-allyl intermediate with the nucleophiles according to Scheme 1 is:
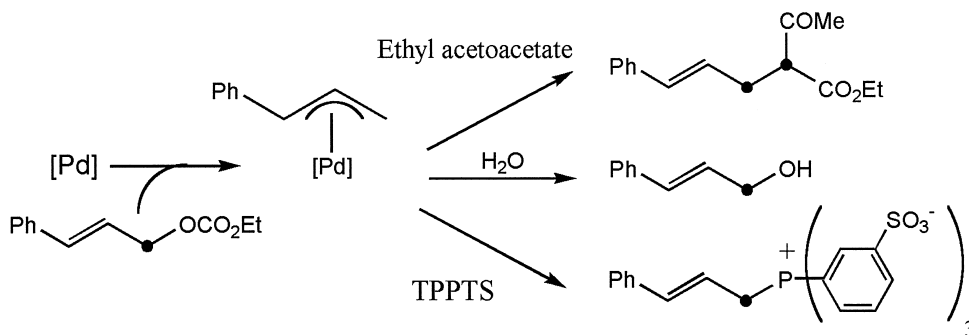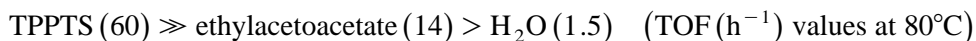
$$\text{TPPTS} (60) \gg \text{ethylacetoacetate} (14) > \text{H}_2\text{O} (1.5) \quad (\text{TOF} (\text{h}^{-1}) \text{ values at } 80°C)$$

Scheme 1.

Table 2
Influence of the reaction medium on the catalyst activity and selectivity

Reaction medium	Ratio substance/Pd		Time (h)	Conversion (%)	TOF (h^{-1})	Yields (%)[d]		
	Overall[c]	BMICl				Monoalk	Alcohol	missing[e]
BuCN/water (see Fig. 1)	11	–	9.3	89	0.5	38	10	42
BuCN/water (80°C)	11	–	2	100	3.6	65	11	24
BuCN/water + MeCN (20%)[a]	13	–	8	97	0.9	56	17	27
BuCN/water + EtOH (4%)[a]	11	–	7	97	0.8	50	12	35
BuCN/water + TPP (0.5)[b]	11	–	5.1	100	1	48	10	42
MeCyH/BMICl	11	2.5	1.5	100	5.6	76	0	24
MeCyH/BMICl	34	5.6	1.7	100	18	89	0	11
MeCyH/BMICl (80°C)	37	2.8	1.4	100	23	90	0	10

[a] Total vol.%.

[b] Molar ratio TPP/Pd (TPP is triphenylphosphine).

[c] Defined as the total molar ratio between the substrate and the palladium introduced.

[d] Total yields. For the tests involving the aqueous layer, the aqueous phase concentration is neglected. For the tests involving the molten salt, the actual final concentrations in both phases have been determined.

[e] Mass balance default based on the cinnamyl group. It includes the bis alkylated side product (1 to 5% estimated from GC analysis) and the cinnamyl phosphonium. Other conditions: see Fig. 1. MeCyH stands for methylcyclohexane.

In order to solve these selectivity and activity problems, the addition of co-solvents and a co-ligand as reported in the literature has been tested (Table 2). No noticeable effects were observed on the rate of production of the desired product nor on the decrease of the side products formation. Thus, in order to answer, at least, the first question, the catalytic reaction was tested in an aprotic medium. An ionic liquid phase rather than perfluorinated or polyethyleneglycol (PEG) liquids was chosen. The ionic nature of these liquids, evidenced by their electrochemical properties [27,28], should help both to dissolve and to maintain the ionic Pd/TPPTS complex in the catalytic layer. The salt butylmethylimidazolium chloride was tested at first glance because it is easily prepared and melts at 55°C, a temperature compatible with the conditions of the study. As expected, the formation of cinnamyl alcohol was stopped (Table 2).

Surprisingly, a tenfold increase in the rate of reaction was observed. That is simply attributed to the better solubility of the substrate into the ionic liquid. Indeed, estimation of the partition coefficients provides values of 1.6 ± 0.5, 0.5 ± 0.2 and 1.5 ± 0.5 for of the substrate ethyl cinnamyl carbonate, the reagent ethyl acetoacetate and the product ethyl cinnamyl acetoacetate, respectively. Thus, depending on the volume ratio of the two phases methylcyclohexane and BMICl, between 10 and 30 mol% of the organics are actually dissolved in the molten salt layer. That allows to work at overall substrate/palladium ratio as high as 37 which minimises the yield of the phosphonium side product down to ca. 6% (^{31}P NMR) (Table 2). A further advantage of the ionic liquid arises from the possibility of using, as the organic layer, solvents as common as alkanes whereas in the aqueous biphasic systems, nitriles are required for the stabilisation of the catalyst [25].

4. Conclusion

This work describes the identification of side reactions in the Trost–Tsuji C–C coupling of cinnamyl carbonate with ethylacetoacetate and presents the use of the ionic liquid 1-butyl-3-methylimidazolium chloride as a catalytic liquid phase for the reaction. Besides the easy separation of the catalyst, the use of this ionic liquid is fourfold: (i) it dissolves the organic reagents very well which

allows to work at higher substrate/catalyst ratio; (ii) it dissolves palladium chloride which can be used as a Pd(0) precursor instead of the more expensive Pd(acetate)$_2$; (iii) it suppresses the formation of cinnamyl alcohol coming from the side reaction involving water as a nucleophile; and (iv) it allows the use of simple alkanes solvent as the organic layer instead of nitriles. The drawback of the high solubility of the organic compounds in the ionic liquid phase is the recovery of the product(s) of the reaction when operating batchwise. Catalytic tests in a continuous reactor are in progress, both to evaluate the catalyst deactivation and the product separation. The possible use of the deprotonated form of the 1-butyl-3-methylimidazolium cation described as a carbene ligand which would leads to phosphine free catalytic systems is currently investigated [29].

Acknowledgements

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